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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/519,148	LIPSHUTZ ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *80-125* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *80-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/4/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The specification is objected to as documents have been improperly incorporated by reference. In particular, the specification states at page 47, last paragraph:

> In addition, the present invention is further described by reference to the attached appendix. All publications and patent documents cited in this application are incorporated by reference in their entirety for all purposes to the same extent as if each individual publication or patent document were so individually denoted.

Such omnibus language fails to specify what specific information applicant seeks to incorporate by reference and similarly fails to teach with detailed particularity just where that specific information is to be found in each of the cited documents. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

Accordingly, the cited documents are not considered to have been properly incorporated by reference and as such, have not been considered with any effect towards their fulfilling, either in part or in whole, the enablement, written description, or best mode requirements of 35 USC 112, first paragraph.

Response to argument

2. At page 16 of the response received 04 March 2004, hereinafter the response, assert, "[T]he present application clearly identified with particularity what specific material it incorporated."

3. The above argument has been fully considered and has not been found persuasive towards the withdrawal of the objection to the specification. It is noted that this argument is unsupported by a showing of evidence that supports the position proffered. Attention is directed to MPEP 2145.

> Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.
> The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

4. A review of the disclosure finds numerous occurrences where multiple documents are cited as teaching various aspects. For example, the following passages are found on pages 11 of the specification.

amplification of a targeted nucleic acid sequence. These amounts are readily determined from known PCR protocols. See, e.g., Sambrook, et al. *Molecular Cloning: A Laboratory Manual*, (2nd ed.) Vols. 1-3, Cold Spring Harbor Laboratory, (1989) and *PCR Protocols: A Guide to Methods and Applications* (Innis, M., Gelfand, D., Sninsky, J. and White, T., eds.) Academic Press (1990), both of which are incorporated herein by reference for all purposes in their entirety. For those embodiments where the various reagents are

As seen above, the citation is simply bibliographic in nature and does not direct the public with any degree of particularity to any one or more parts of the cited documents, or even a particular volume. In contrast, applicant at page 19 of their response, direct attention to various chapters of Molecular Cloning. Such later-filed disclosures can not and do not make up for the failure of the originally filed specification to teach with detailed particularity what material applicant seeks to incorporate by reference and where that information is to be found in each of such documents.

5. Argument is advanced that a Ph.D. in the relevant art would intuitively know what material is being incorporated by reference and would also be able to find it in each of the cited documents. Such argument is conclusory. MPEP 2145. Further, the record does not establish how any individual of any skill level would be able to understand which portion(s) of the various documents are relevant to any conceivable purpose when they have been incorporated "for all purposes."

6. Argument is advanced that the present application and its disclosure is nonanalogous to the cited decisions as found in the Office action of 17 July 2003, as well as hereinabove. This argument has been fully considered and has not been found persuasive as none of the cited decisions support the position that applicant does not need to disclose their invention. It is further noted that the USPTO notified the public at 1145 TMOG 361, left column:

> Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found.

As noted above, the original specification, unlike applicant's remarks as found at page 19 of the response, do not teach which specific portions of the referenced documents the incorporated subject matter can be found. Therefore, and in the absence of convincing g evidence to the contrary, the objection to the specification is maintained.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 80-125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the

invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

9. Independent claims 80, 93, 106, and 107 are all drawn to "[a] method of analyzing a sample." Each of said claims require the detection and evaluation of a signal through the use of confocal microscopy, and in the case of claims 80 and 93, hybridization is to have taken place prior to the signal being detected and evaluated. In accordance with the recited method steps, and using claim 80 as an example for the remaining independent claims, one is to perform two method steps prior to performing said confocal microscopy. One of the method steps is to be performed in a first chamber and the second method step is to be performed in a second chamber. The first method step can be "a preparative reaction, an analysis reaction, sample acquisition, DNA extraction, amplification, IV transcription or labeling" and the second method steps can be "a preparative reaction, an analysis reaction including hybridization, sample acquisition, DNA extraction, amplification, IV or labeling." In view of the choices presented, the claims are considered to encompass performing "sample acquisition" in the first chamber and "DNA extraction" in the second chamber and there never take place any hybridization reaction, much less the incorporation of a label that would produce a signal that would be detected by confocal microscopy being practiced from without the device when extracted and unlabeled and

unhybridized DNA is within the device. Other combinations, still not requiring any hybridization or any label, are also encompassed.

10. The specification does not set forth a reproducible procedure whereby the unhybridized and unlabeled can be detected and a signal produced from that which is incapable of producing a signal, can in turn be analyzed such that any meaningful determination be made about the sample under investigation.

11. The specification discloses three examples:

- Example 1- Acoustic Mixing (pages 44-45),
- Example 2- RNA Preparation Reaction in Miniaturized System (pages 45-46), and
- Example 3- PCR Amplification in Miniaturized System (pages 46-47).

None of these examples disclose starting materials and reaction conditions where a first reaction chamber and second reaction chamber are used to perform the defined reactions, and to then perform confocal microscopy on a hybridized sample and then make any analysis of the results. In short, it appears that applicant is trusting in the ability of the public to determine the operational parameters so to enable the claimed method and related device. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****

> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. <u>However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.</u> It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

12. The level of skill in the art is considered to be high, on par with those that hold a Ph.D. in biochemistry and have several years of laboratory experience. Such high level of experience, however, is offset by unpredictability in the art.

13. As presently worded, the claimed methods are considered to encompass performing and analysis of physiological and chemical conditions which are recognized as being unpredictable. In support of this position, attention is directed to the decision of *Vas-Cath Inc. v. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain

> how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Additionally, the claimed method relates to the use of devices that have fluid connections, which present additional issues of enablement. The art recognizes numerous difficulties associated with junctions in a device intended for fluid manipulation. As set forth in Shartle et al., (US Patent 5,230,866):

> A number of factors contribute to the instability of the junction. For example, variations in the sample physical properties (such as density, viscosity, hematocrit, microheterogeneity, surface tension, and contact angle with housing wall) can affect both the forward pressure acting to favor flow and the backpressure available at the stop-flow junction to stop flow. Density controls the hydrostatic pressure at the junction. Surface tension and contact angle determine the pressure that the junction can exert in opposition to flow. Viscosity determines the rate at which the sample moves to the junction and therefore the excess back pressure (over that necessary for an equilibrium state) required to prevent the momentum of the sample from breaking through the junction. Hematocrit of blood sample affects both viscosity and density. Microheterogeneity has an impact on local properties at the junction, which can vary significantly from the bulk properties of the sample. Other variations include sample volume, which affects hydrostatic pressure by varying the height of the upper sample surface above the junction; method of sample application by different uses [*sic*; users] (or by the same user at different times); variation from lot to lot of the physical properties, such as contact angle with a standard liquid, of the housing out of which the diluter is made; variations in the size and shape of the junction arising during manufacturing, such as can be caused by plastic "burrs" at corners and edges, and local external factors, such as mechanical vibrations caused by nearby machinery of the diluter from a horizontal operating position.

The specification is effectively silent as to how these art-recognized issues are to be overcome.

14. The art to which the invention relates, i.e., nucleic acid array art and hybridization art, has advanced to the point that certain problematic areas have been identified. In support of this position as it relates to the manufacture and use of oligonucleotide arrays, US Patent 6,077,674 (Schleifer et al.) addresses certain highly problematic areas:

While in situ synthesis is a very flexible means for producing DNA arrays, the fidelity or percentage of full-length oligonucleotides synthesized within a feature on the array is less than 100 percent. An ideal array will have only full-length oligonucleotides attached to each feature. The ideal array promotes accuracy in hybridization experiments or assays or target biological materials. If the fidelity of an in situ generated array is less than 100 percent, it typically has non full-length oligonucleotides within a feature that usually consists of shorter lengths of the correct sequence, and to a lesser degree, incorrect sequences. Typical DNA coupling efficiencies are around 97 to 99 percent for the standard phosphoramidite chemistry. For oligonucleotides that are 25 nucleotides in length, these efficiencies result in only 46 to 77 percent full-length oligonucleotides contained within a feature (0.97^{25} to 0.99^{25}). This loss of fidelity can cause chemical noise in hybridization conditions. The loss of fidelity can also lead to difficulty in interpreting the data.

Photolithography is a method used by Affymetrix in California to produce in situ arrays using procedures that are similar to those used in the semi-conductor industry. In procedure described by Fodor et al. from Affymetrix U.S. Pat. No. 5,405,783, a photo-deprotection step is used where the protecting group on the phosphoramidite is removed by exposing a photosensitive protecting group to light. Four photo masks are used to create patterns to de-protect areas of the substrate and then a nucleotide is added to these regions. This technique requires four masks for each layer of nucleotides. While this technique allows for the production of high-density oligonucleotide arrays, it is less efficient than traditional phosphoramidite synthesis chemistry. With efficiencies of about 90 to 95 percent, the percentage of full-length oligonucleotides within a feature is further reduced to about 9 to 27 percent for oligonucleotides that are 25 nucleotides long (0.90^{25} to 0.95^{25}).

15. Carrico, (US Patent 5,200,313) similarly identifies problematic aspects of hybridization reactions:

1. The purity of the nucleic acid preparation.

2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no

specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

16. In view of the innumerable art-recognized difficulties, the limited disclosure, and the absence of convincing evidence to the contrary, the pubic would be forced to conduct undue experimentation in order to practice the full scope of the invention, assuming that such a goal could even be attained. Accordingly, claims 80-124 are rejected under 35 USC 112, first paragraph, as not enabled by the disclosure.

17. *Response to argument*

18. At page 19 of the response applicant asserts that the claimed invention is enabled by the disclosure, noting that one of skill in he art would have to not only rely of cited publications, but would also have to rely upon their innate ability to identify which part or parts of the various publications are germane to a given element of the claimed invention and would then be able to readily extrapolate from these teachings the asserted non-obvious invention. In support of this position, applicant's representatives directs attention to various chapters of Molecular Cloning, chapters that were not identified a relevant in the original specification.

19. This argument has been fully considered and has not been found persuasive towards the withdrawal of the rejection. As noted above, the cited documents have not been properly incorporated by reference and as such they cannot be relied upon for satisfaction of either enablement, written description, or best mode requirements of 35 USC 112, first paragraph. While applicant now directs attention to relevant portions of at least one such publication, such does not overcome the deficiency of the originally filed specification.

20. At page 20 of the response argument is advanced that the claimed method is not directed to a method of producing a protein or producing a gene or any specific biological polymer but

are instead directed to analyzing a sample in an integrated microfluidic device, and as such the decisions in *Genentech* and in *Amgen* are nonanalogous.

21. The above argument has been fully considered and has not been found persuasive. In contrast with applicant's assertions, the claimed method does in fact require the production of specific biological polymers as such is reflected in requiring one to conduct amplification reactions. Indeed, the claimed method fairly encompasses performing nucleic acid amplification (see claim 80, line 13) on the very nucleic acid sequences that were held not to be disclosed in *University of California v. Eli Lilly and Co.* (CA FC, July 1997) 43 USPQ2d 1398.

22. Agreement is reached in that the Federal Circuit has required heightened standard of enablement due to predictability of the biotechnology art. As shown above, the art has advanced to the point where various problematic areas have been identified. The claimed invention fairly encompasses just such areas yet neither teaches outright, or through a valid incorporation by reference, how such problematic areas are to be overcome. Absent such guidance, the ordinary artisan is forced to resort to undue experimentation. *Genentech*.

23. Argument is advanced at page 21 that the problems identified in US Patent 5,230,866 (Shartle et al.) are not applicable to the present invention as they had been resolved prior to the filing of the instant application.

24. The above argument has been fully considered and has not been found persuasive. It is noted with particularity that applicant, at page 19 of their response directs attention to various chapters of Molecular Cloning as enabling virtually all aspects of the claimed invention, yet Molecular Cloning was published in 1989, which is significant as it predates Shartle et al., by some four years. Understandably, Molecular Cloning does not even identify, much less resolve

the issues of non-enablement taught by Shartle et al. Accordingly, the very documents that applicant seeks to rely upon for enablement do not and cannot teach how art-recognized problems (Shartle et al.) are to be overcome and as such the disclosure. Assuming *arguendo*, that the disclosure did include documents improperly incorporated by reference, such documents do not enable the claimed invention as they fails to teach essential aspects of how art-recognized issues are to be overcome.

25. At page 21, bridging to page 22, applicant does not disagree with the teachings of US 6,077,674 (Schleifer et al.), yet asserts that the claimed method is not directed to the manufacture of full-length oligonucleotide arrays and as such issues of manufacture and use are not applicable to the claimed invention.

26. The above argument has been fully considered and has not been found persuasive towards the withdrawal f the rejection as the claimed method fairly encompasses using a device that comprises full-length oligonucleotide arrays. Additionally, the claimed methods explicitly recite that the artisan is to perform amplification reactions, which in turn require the use of enzymes. As a result of having to perform such steps, the artisan would be facing the same issues of incomplete transcripts (processivity) as well as incorrect nucleotide sequences (fidelity) that are encountered with respect to synthesizing the required primers. In view of such issues, the teachings and problems described by Schleifer et al., are in fact extremely relevant to the issue of the instant claims not being enabled by the disclosure and as such, the rejection is maintained.

27. Argument is advanced that the issues enumerated by Carrico are not relevant to the claimed invention as the publication of Carrico was within the public domain at the time of the filing of the instant application.

28. The above argument has been fully considered and has not been found persuasive towards the withdrawal of the rejection, as the claims are not limited to those specific embodiments that Carrico teaches and claims. Rather, the claimed invention fairly encompasses embodiments that Carrico teaches as being non-enabled. In view of the breadth of scope of the claims, the art-recognized unpredictability, and the limited guidance provided by the disclosure, claims 80-125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

29. Claims 80-125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification has been found, at best, to provide only a guide or suggestion as to how the claimed method is to be practiced. The disclosure and indeed the examples do not set forth starting materials and reaction conditions under which a single embodiment can be practiced in full and any meaningful analysis result. While applicant may consider that the written description requirement could be satisfied through assertions of obviousness, such is not dispositive of the instant rejection. In support of this position, attention is directed to the

decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

30. In view of the paucity of the disclosure, and the absence of convincing evidence to the contrary, claims 80-125 are rejected under 35 USC 112, first paragraph, as it relates to written description.

Response to argument

31. A review of the response of 04 March 2004 fails to locate a specific traversal of the written description rejection, however, it appears that such traversal may be interspersed in the traversal to the rejection of claims under 35 USC 112, as it relates to the enablement requirements. As noted above, the specification, even in light of arguments found in the response, has not been found to provide either an enabling disclosure nor an adequate written description of the invention, including the requisite starting materials. Accordingly, and in the absence of convincing evidence to the contrary, the rejection is maintained against claims 80-124 and is also applied against new claim 125.

32. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

33. Claims 80-125 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims fail(s) to

correspond in scope with that which applicant(s) regard as the invention can be found in Paper No. 2 filed 06 March 2000. In that paper, applicant stated that new claims are being added via a preliminary amendment whereby the claims are drawn to a method and not to a device, and this statement indicates that the invention is different from what is defined in the claim(s) as al of the original claims were drawn to a device, not a method. Further, a review of the disclosure fails to find support for methods having been considered, at the time of filing, to be the invention. In support of this position, attention is directed to the following portions of the disclosure, starting with the title:

Attorney Docket No.: 18547-009911

PATENT APPLICATION

INTEGRATED NUCLEIC ACID DIAGNOSTIC DEVICE

Inventors:

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SUMMARY OF THE INVENTION

The present invention generally provides miniature analytical devices that include a plurality of distinct reaction chambers disposed in a single, miniature body.

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DESCRIPTION OF THE SPECIFIC EMBODIMENTS

I. General

It is a general object of the present invention to provide a miniaturized integrated nucleic acid diagnostic device and system. The device of the invention is generally capable of performing one or more sample acquisition and preparation operations, in combination with one or more sample analysis operations. For example, the device can integrate several or all of the operations involved in sample acquisition and storage, sample preparation and sample analysis, within a single, miniaturized, integrated unit. The device is useful in a variety of applications and most notably, nucleic acid based diagnostic applications and *de novo* sequencing applications.

The device of the invention will typically be one component of a larger diagnostic system which further includes a reader device for scanning and obtaining the data from the device, and a computer based interface for controlling the device and/or interpretation of the data derived from the device.

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III. The Nucleic Acid Diagnostic System

A. Analytical System

A schematic of a representative analytical system based upon the device of the invention is shown in Figure 1. The system includes the diagnostic device 2 which

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B. The Diagnostic Device

As described above, the device of the present invention is generally capable of carrying out a number of preparative and analytical reactions on a sample. To

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As described herein, the overall geometry of the device of the invention may take a number of forms. For example, the device may incorporate a plurality of

and

the abstract:

INTEGRATED NUCLEIC ACID DIAGNOSTIC DEVICE

ABSTRACT OF THE DISCLOSURE

The present invention provides a miniaturized integrated nucleic acid diagnostic device and system. The device of the invention is generally capable of performing one or more sample acquisition and preparation operations, in combination with one or more sample analysis operations. For example, the device can integrate

34. All of the above examples state that the invention lies in the device. While the specification disclose methods of using the device, such teachings are considered an attempt at fulfillment of the enablement requirement under 35 USC 112, first paragraph, and do not imply that applicant, at the time of filing, considered the invention, in whole or in part, to lie in a method of using any device. It is further noted that the subject application was filed on even date with a preliminary amendment yet the declaration filed did not reflect that the subject application was effectively amended, i.e., the instant application was a continuation-in-part. If such had been effected at the time of filing the instant rejection would have been moot. As filed, however, the original disclosure has not been found to support the position that applicant considered method claims to be their invention. Accordingly, and in the absence of convincing evidence to the contrary, claims 80-125 are rejected under 35 USC 112, second paragraph.

Response to arguments

35. At page 23 of the response argument is presented that the specification provides support for the notion that the invention lies in a method of conducting an assay and not just in a device. In support of this position, attention is directed to page 5, lines 20-26, of the specification. Applicant also directs attention to the newly amended title of the application as further evidence that the specification supports the presently claimed invention.

36. The above argument has been fully considered and has not been found persuasive towards the withdrawal of the rejection. While the specification may contain statements of intended usefulness of a device, such is not to say that applicant contemplated an embodiment of the invention actually being a method of performing an assay. As evidenced in the prior Office action and reproduced above, the specification does teach at length that the invention is a device. While applicant now amends the title of the application to where it is directed to a totally different invention, such does not alter the fact that such teachings are not to be found in the original disclosure. Therefore, and in the absence of convincing evidence to he contrary, the rejection is maintained.

Claim Rejections - 35 USC § 103

37. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

38. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

39. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

40. Claims 80-110, 112-114, and 116-125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilding et al., (US Patent 5,304,487; hereinafter "Wilding 1"), in view of Staecker et al., and Wilding et al., (US Patent 5,587,128; hereinafter "Wilding 2").

41. Wilding 1 discloses a method for analyzing a sample in an integrated microfluidic device that has a plurality of chambers that are in fluid communication with each other. As seen in column 2, the diameter of the channels can range from 0.1 μm to 500 μm. Said channels are in communication with "fluid handling regions." Said regions are considered to meet the limitation of applicants "at least two chambers." Column 3 discloses that the results can be detected through a window, and that such detection includes the use of detectable moieties. Column 9

discloses the optional use of additional components for detecting/viewing the assay results. The aspect that the resultant signal can be viewed through a window is considered to meet the limitation that the "reader" is outside of the chamber (a limitation of independent claims 80 and 93, and claims 81-92, 94-105, 110-125 that depend therefrom).

42. Column 4, first paragraph, teaches explicitly of the optional use of valves within the fluid communication means.

43. The use of the device in the analysis of nucleic acids, be it DNA or RNA is explicitly taught at column 6. The use of detectable moieties in combination with DNA probes, as in nucleic acid assays, is disclosed at column 7.

44. Wilder 1 does not disclose the use of confocal microscopy; nor the use of electrophoretic separation of nucleic acid fragments.

45. Wilding 2, which is based upon a CIP application that matured into Wilding 1, teaches the use of the device in the analysis of nucleic acids, including the amplification of sequences. The use of arrays in concert with the detection of target sequences is disclosed (column 24).

46. While Wilding 2 does teach the use of readers/detection means that are placed internal to the device, it is also noted that Wilding 2 explicitly teaches that one can detect the signal, e.g., a fluorescent signal, "either visually or by machine, through a transparent window disposed over the detection region." At column 19, lines 18-20, each explicitly that the device may comprise a microscope to view contents within the device.

47. Wilding 2, column 20, penultimate paragraph, teaches performing electrophoretic separation of nucleic acid sequences. The performance of electrophoretic separation speaks directly to separating the nucleic acid sequences according to size.

48. As noted above, Wilding 1 discloses using valves. Wilding 2, column 24, teaches:

> In one embodiment, flow systems of the device may be maintained at a hydraulically full volume, and valves in the appliance, or alternatively, in the device, may be utilized to direct fluid flow. (Emphasis added)

Such a teaching is considered to render obvious the inclusion and use of valves at any and all places within the fluid flow channel where an artisan may wish to control and direct fluid flow.

49. Wilding 2 does not teach the use of confocal microscopy, yet, as noted above, does teach performing microscopy.

50. Steacker et al., teach of an assay wherein nucleic acids are subjected to amplification and the resultant amplification product is detected/studied through the use of confocal microscopy.

51. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method and device of Wilder 1 and Wilder 2 so to utilize confocal microscopy as taught by Steacker et al. Motivation for performing confocal microscopy on an amplification product is found at page 76, right column, where it is taught that this procedure allows for the detection of minute quantities of mRNA and avoids the time-consuming process of autoradiography.

52. Claims 111 and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilding 1, Wilding 2, and Staecker et al., as applied to claims 80-110, 112-114, and 116-125 above, and further in view of Brelje et al.

53. Brelje et al., teach at length of the advantages of performing scanning confocal microscopy, including where nucleic acids are being studied. Table 2, column 10, teaches

explicitly of DNA specific stains (Chromomycin A3) as well as the use of fluorescein the same fluorophores used by Staecker et al.

54. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Wilder 1, Wilder 2, and Staecker et al., with the method of Brelje et al., so that scanning form of confocal microscopy was used. As set forth in columns 1 and 2, confocal microscopy is well known in the art, yet the aspect of performing scanning confocal microscopy has been found to improve on the design of confocal microscopy. In view of the explicit guidance to use scanning confocal microscopy, and in view of the well-developed nature of confocal microscopy as well as performing nucleic acid assays in integrated microfluidic devices, the ordinary artisan would have been both sufficiently motivated and expectant of success in performing such a combination.

55. For the above reasons, and in the absence of convincing evidence to the contrary, the invention of claims 80-124 is considered to be obvious in view of the prior art of record.

Response to argument

56. At pages 23-27 of the response argument is presented that the prior art does not provide adequate motivation for using confocal microscopy, that the prior art does not each having valves between chambers, stressing at page 27 that the limitation of placing a valve in the flow path between channels is not suggested.

57. The above arguments have been fully considered and have not been found persuasive towards the withdrawal of the rejections. As disclosed above, Wilding 2 teaches explicitly that contents within a channel can be viewed via a microscope. Such teaching speaks directly to one being able to view within the device. With Staecker et al., teaching nucleic acids are subjected to

amplification and the resultant amplification product is detected/studied through the use of confocal microscopy, one would have been amply motivated to apply confocal microscopy for viewing the same reactions in a device known to be viewable via microscopy.

58. The aspect of placing valves between chambers of the device, as noted above, are in fact disclosed by the prior art of record Wilding 2, column 24, teaches:

> In one embodiment, flow systems of the device may be maintained at a hydraulically full volume, and valves in the appliance, or alternatively, in the device, may be utilized to direct fluid flow. (Emphasis added)

Such a teaching is considered to render obvious the inclusion and use of valves at any and all places within the fluid flow channel where an artisan may wish to control and direct fluid flow.

59. In response to applicant's argument that the examiner has combined an excessive number of references (page 25 of the response), reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

60. For the above reasons, and in the absence of convincing evidence to the contrary, the rejection of claims under 35 USC 103(a) is maintained.

Conclusion

61. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

62. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

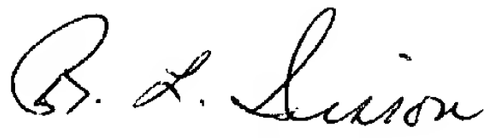
MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

63. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

64. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

65. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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